REMARKS

Claims 36 and 40 have been amended to clarify the claims. Support for the addition of "reduces and/or" in the claims is provided in the last page of the summary of the invention. No new matter has been added.

Rejection Under 35 U.S.C. § 112

A. The Examiner has rejected claims 36, 39, 40 and 44 under 35 U.S.C. §112, first paragraph as containing subject matter not adequately described in the specification so as to enable one skilled in the art to practice the invention.

The Examiner has set forth Wands factors in making the rejection. Applicant responds as follows to the assertions made in the recitation of the Wands factors.

1. Breadth of the claims

The Examiner alleged that the claims constitute a "wish to know compounds" and that the "scope of potential compounds is unlimited" (Office Action at 4). Applicant respectfully disagrees. The compounds recited in the claimed method are quite clearly limited by their binding to the ATP binding site of MLK. As is discussed in greater detail below, the ATP binding site of MLK was known and therefore the parameters of compounds could be determined by one of ordinary skill in the art based on the structural constraints imposed by the protein structure.

2. State of the art/Level of skill in the art/Level of unpredictability

Applicant agrees that the level of skill in the art is high.

The Examiner provided a lengthy discussion of the alleged uncertainties in the prior art. Applicant respectfully disagrees. Any uncertainties mentioned by the Examiner are quite clearly

normal in science. As the Examiner undoubtedly knows, authors of scientific articles rarely if ever make absolute claims or expressions of certainty. The ordinary expressions are those highlighted by the Examiner: one postulates and makes hypotheses that are testable, even if absolute proof is lacking. But absolute proof is not the standard required for enablement. 90% of the synapses in the brain produce glutamate. When neurons are degenerating, the production and the release of glutamate are dysregulated, which results in overproduction of glutamate and excitotoxicity. Inhibition of MLK will protect neurons from insult induced by over-production of glutamate or excitotoxicity.

Parkinson's disease is a human disease. Transgenic mice generated by using a mutant human gene isolated from patients with Parkinson's disease do not have the disease phenotype. This is also true for animal models for other neurodegenerative diseases such as Huntington's and Alzheimer's diseases. However, these mutant genes cause cell death in cultured neurons and in the brains of transgenic mice. Humans can live 100 years and mice only have two-year life spans. The neuronal death process in human is much slower than that in mice. Regardless how these mutant genes cause neurons to die, when neurons are slowly dying or degenerating, there is over-production of glutamate and an MLK inhibitor can protect neurons from excitotoxicity and slow down Parkinson's disease or other neurodegenerative disease.

Applicant does disagree with the Examiner's contention on page 6 of the Office Action that no clear link is made between neurodegenerative disease and excitotoxicity. That link quite clearly has been established in the art, and in fact was recognized and cited by the Applicant in the first paragraph of the instant application.

The Examiner also commented on certain deficiencies in correlation between animal models and *in vitro* tests. (Office Action at 10-11). As a result of these alleged deficiencies, the Examiner concludes that because the availability of relevant model systems is not established, that the level of unpredictability in the art is high.

Applicant respectfully disagrees. The purported lack of establishment of the availability of model systems is both incorrect and not indicative of a highly unpredictable art. There quite clearly are model systems that, while perhaps not perfect, have been used in the relevant art for many years. Most in vitro and animal models of disease do replicate exactly the disease, but are

important for testing compounds to determine whether such compounds are suitable for human clinical trials, and are commonly used for such a purpose. The standard for enablement is that the description in the application must be such that one of ordinary skill in the art would not have to conduct undue experimentation. If there are well-established model systems, then by using such model systems, the skilled person must be practicing only routine experimentation.

Regarding the discontinuation of the clinical trial for one MLK inhibitor, CEP-1347, this decision of the sponsors of the trial is not necessarily indicative of a lack of clinical effect of that compound, or more importantly, the class of MLK inhibitors. Nor is clinical efficacy of this one compound determinative of the level of unpredictability.

In contrast to the Examiner's conclusion that the art is unpredictable, the indications from the literature of both standard animal models and tests of MLK inhibitors are that the predictability of the art is sufficiently high so that only routine experimentation is required to practice the claimed invention. It must be remembered that selecting a compound for human therapeutic use is a lengthy process, which may involve years of testing (in vitro, models and clinical), but this is the routine procedure followed in the art, and therefore must be considered to involve only routine experimentation. As such, this element of the Wands analysis should not be considered a bar to enablement.

3. Amount of direction/Working examples

The Examiner reiterates that Applicant did not provide an example of blocking ATP binding to MLK. Applicant respectfully disagrees.

It cannot be said that direction is not provided when a working example that specifically includes a biochemical mechanism is included in a patent application. Specifically, Example 3 (Role of MLK in Neuronal Apoptosis) describes the use of a "kinase dead" MLK2, which has been rendered so by a point mutation to the ATP binding loop of the MLK2 kinase domain (resulting in an amino acid substitution of K to E). This mutation is specific for ATP binding by MLK2, and as is well known in the art, kinases that cannot bind ATP (the phosphate donor) cannot transfer phosphate to their cognate substrates (e.g., SEK1 for MLK). In case there was

any doubt about this point, Applicant explicitly stated that this "point mutation leads to total loss of kinase activity of MLK2." Therefore, the mutant MLK2 used in the working example is one that cannot bind ATP, and this can be viewed as an equivalent of MLK2 inactivated by inhibitor binding. It is true that this molecule, by itself, is not a teaching of an inhibitor molecule that binds to the ATP binding site of MLK. However, to the person of skill in the art, this is a clear teaching that inhibitors that bind the kinase domain ATP binding site would be effective in inhibiting the activity of the molecule and in having the downstream effects on biochemical pathways important in neurodegenerative diseases, particularly Parkinson's disease.

The Examiner's stated on page 11 of the Office Action that no guidance was provided regarding the binding pocket of MLK. This cannot be true, for the reason stated above: Applicant used a MLK molecule with a specific mutation to the ATP binding loop, which necessarily is in the ATP binding pocket.

Persons of skill in the art were very familiar with compounds that bind to ATP binding pockets of kinases, thereby inhibiting them. One of these, K-252a, was a recognized protein kinase inhibitor that acts on the nerve growth factor pathway (Hashimoto, J Cell Biol, 107:1531-1539, 1988). K-252a was known to interact with kinases at ATP binding domains (see, e.g., Nakashini et al., J Biol Chem, 263:6215-6219, 1988). Moreover, a derivative of this compound, CEP1347 (also known as KT 7515) was shown to inhibit motoneuron apoptosis (Maroney et al., J Neurosci, 18:104-111, 1998), which effect was later demonstrated to be the result of inhibition of MLKs (Maroney et al., J Biol Chem, 276:25302-25308, 2001). Therefore, the person of skill in the art was familiar with kinase inhibitors that bind to ATP binding domains.

The specification guides one skilled in the art to investigate compounds that inhibit the kinase activity of MLKs, particularly those that interfere with ATP binding to the kinase domain of MLKs. Accordingly, in view of the knowledge in the art and the guidance offered in the specification, one of ordinary skill in the art would not have had to practice undue experimentation based on the amount of direction or working examples provided in the specification. In fact, the guidance in the specification would have led one of ordinary skill in

the art to compounds such as K-252a and CEP-1347, such as by routine screening of known kinase inhibitor compounds.

Thus in contrast to the Examiner's assertion that no guidance was provided for narrowing the "universe of all possible compounds", the specification quite clearly did guide the skilled person to those compounds that interfere with ATP binding to kinase domains. Since the amino acids of the MLK kinase domains were known to the skilled person, the types of structures that would be likely to bind to the domains and block ATP binding also were known. Alternatively, the skilled person could initiate screening of known inhibitors of kinases. Based on their structures (for example, the indolocarbazole structure of K-252a that was known in the art), the skilled person would not have to engage in undue experimentation to identify suitable compounds.

The identification of suitable compounds might require a significant amount of experimentation, but such experimentation is not undue if it is the sort practiced in the art. This is analogous to the situation in Wands, in which monoclonal antibody-secreting hybridomas were screened. In re Wands, 858 F.2d 731(Fed. Cir. 1988). Two of the factors used by the court to decide in favor of enablement in the Wands case are equally applicable here: all of the methods needed to practice the claimed invention were known, and there was a high level of skill in the art. As explained above, Applicant asserts that sufficient guidance was provided to guide the skilled artisan to kinase inhibitors.

Regarding the Examiner's statements on page 14 of the Office Action that one of ordinary skill in the art would "have to establish the relevance of a particular animal model" and "have a reasonable expectation that the studies with the animal model would extrapolate to human disease", Applicant respectfully requests that the Examiner consider the long-term use of animal models of Parkinson's disease as sufficient evidence that the animal models known to one of ordinary skill in the art were both relevant and reasonable for extrapolation to human disease. If the Examiner believes that the models are not so, then Applicant respectfully requests that the Examiner provide evidence to support the assertions. Applicant knows of no evidence that the skilled person would have believed anything other than that the models were both relevant and

reasonable to extrapolate. If the models were not, then Applicant submits that persons of skill in the art would not be using models as the use of such models would be a waste of resources and time.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejection of the claims made under 35 U.S.C. §112, first paragraph, as not enabled.

B. The Examiner has rejected claims 36, 39, 40 and 44 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement.

New matter

The Examiner indicated on pages 14-15 of the Office Action that the recitation of compounds that block binding of ATP to a MLK ATP binding site is new matter. The Examiner discusses the alleged shortcomings of the link between excitotoxicity and neurodegenerative diseases. Applicant respectfully requests reconsideration.

Assuming that the Examiner's rejection is based on the previous amendment to the claims (the recitation of compounds that block binding of ATP to a MLK ATP binding site), then Applicant's reply is that persons skilled in the art would have recognized that the application as filed described the now-claimed invention, such that the amendment is not new matter. In particular, the recitation in Example 3 of the mutation of the ATP binding site, in combination with the disclosure in the application of MLK inhibitors as compounds that inhibit a MLK protein activity, e.g., a kinase activity (see, e.g., page 12, lines 22-24 and page 21, lines 18-21), is sufficient to indicate to the skilled person that Applicant was in possession of the invention as claimed.

The general requirement for satisfying the written description requirement is that the specification describes the invention in sufficient detail such that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath,

Inc. v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991). In addition, one need not, and preferably does not, describe that which is known.

Applicant asserts that the description in the specification is sufficient for one of ordinary skill in the art to understand that the invention was possessed by Applicant. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Written description

The Examiner rejected the claims as lacking an adequate written description. Applicant respectfully requests reconsideration.

As noted above, the description is adequate if it conveys to one of ordinary skill in the art that Applicant was in possession of the invention as now claimed. Applicant agrees with the Examiner that the level of skill in the art was high.

The Examiner again mentions excitotoxicity in this rejection. Applicant respectfully requests clarification, since this pertains to the cause of neurodegenerative disease, and not the effect of the claimed method. The claimed invention does not indicate that the compounds reduce or prevent excitotoxicity, but instead are inhibitors of the kinase activity of MLKs. The involvement of excitotoxicity in neurodegenerative diseases is besides the point. Similarly, whether one skilled in the art would have an expectation that MLKs have a role in the biochemical mechanisms of neurodegenerative disease is beside the point, because this is the teaching of the application itself.

Applicant does not agree that no partial structure was provided. As described above, the application identified a particular site in the MLK molecule that can be targeted for inhibition. Given the high level of skill and knowledge in the art, the identification of such as site (i.e., the ATP binding site of the MLK kinase domain) provides the skilled person with more than adequate information regarding Applicant's possession of the invention. Methods for designing compounds based on protein structure were well known in the art and were routinely practiced. For just two examples pertaining to kinase inhibitors, see Furet et al., J Comput Aided Mol Des

9:465-472, 1995, and Traxler et al., J Pharm Belg 52:88-96, 1997 (Mar-Apr). These references describe modeling of ATP binding sites and molecules that bind thereto and inhibit kinase activity.

Regarding the Examiner's assertions that the ATP binding site information is functional and not structural (numbers 3 and 4 on page 17 of Office Action), Applicant respectfully disagrees for the reasons noted above. For the skilled person, the identification of the ATP binding site in a known protein as a preferred target, as done by Applicant, is sufficient to indicate what structure is to be targeted. Due to the structural constraints inherent in the three-dimensional protein structure of MLK based on the amino acid sequence, one of ordinary skill in the art would know the structural parameters for inhibitors. For example, the skilled person would know that inhibitor molecules must be sized to bind to the ATP binding site. Thus, the description in the application is by no means merely functional.

Finally, with regard to the method of making the invention section on pages 17-18 of the Office Action, Applicant maintains that the Examiner applies an incorrect and restrictive standard that is not part of the case law. What Applicant has described in the application is not merely a goal that one might achieve. Applicant has described a method of treating a particular disease by using molecules that target a particular site (ATP binding) of particular proteins (MLKs). The description certainly provides to the skilled person the understanding that Applicant possessed the claimed invention. Applicant has provided the required distinguishing identifying characteristics to permit one of ordinary skill in the art to recognize that the invention was made.

This is particularly true in view of the inverse relationship between the level of skill and knowledge in the art (agreed to be high) and the specificity of the disclosure needed to satisfy the written description requirement. Based on Applicant's disclosure, there cannot be any doubt that the skilled person would understand the nature (including structure and effect on ATP binding) of the MLK inhibitors and the use of such inhibitors in treating Parkinson's disease.

Thus, the specification clearly indicates to one of ordinary skill in the art, in view of the knowledge possessed by the person of skill in the art, that Applicant was in possession of the claimed invention. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the written description rejection.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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